Chapter-3

Basic Mechanism Involved in the Process of Inflammation and Repair-I

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Abstract

Inflammation is a complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells, or irritants. It serves as a protective mechanism aimed at removing the injurious stimuli and initiating the healing process. The clinical signs of inflammation, famously described by the Roman physician Celsus, include redness (rubor), heat (calor), swelling (tumor), and pain (dolor), with loss of function (functio laesa) later added by Galen. Inflammation can be classified into two main types: acute and chronic. Acute inflammation is the immediate response to injury, characterized by the rapid influx of immune cells, mainly neutrophils, to the site of injury. Chronic inflammation, on the other hand, is a prolonged response involving lymphocytes and macrophages, leading to tissue destruction and repair simultaneously. The mechanism of inflammation involves a series of complex events, starting with alterations in vascular permeability and blood flow. Upon injury, blood vessels dilate to increase blood flow to the affected area, a process known as vasodilation. This is followed by an increase in vascular permeability, allowing proteins and white blood cells to exit the bloodstream and enter the damaged tissue. These changes are mediated by various chemical signals, such as histamines and cytokines, released by injured cells and immune cells. Understanding these basic mechanisms is crucial for developing treatments that can modulate the inflammatory response and promote effective tissue repair.

I. INTRODUCTION

The process of inflammation and repair is crucial for maintaining tissue homeostasis and responding to injury or infection. Here's a detailed overview of the basic mechanisms involved:

1. Inflammation

Inflammation is a complex biological response to harmful stimuli, such as pathogens, damaged cells, or irritants. Its primary goals are to eliminate the initial cause of cell injury, clear out dead cells, and repair tissue.

Phases of Inflammation:

a. Acute Inflammation

- **Onset:** Rapid onset (minutes to hours).
- **Duration:** Short-lived (minutes to days).
- **Key Features:** Edema (swelling), redness, heat, pain, and loss of function.
- **Mechanisms**
  - **Vascular Response**
    - **Vasodilation:** Blood vessels widen to increase blood flow to the affected area, which helps deliver immune cells and nutrients.
    - **Increased Permeability:** Blood vessel walls become more permeable, allowing proteins and cells to pass into the tissue.
  - **Cellular Response:**
    - **Leukocyte Recruitment:** White blood cells, especially neutrophils, migrate from the bloodstream to the site of injury. This process is guided by chemotactic signals.
    - **Phagocytosis:** Immune cells engulf and destroy pathogens and debris.
  - **Chemical Mediators:** Various chemicals (e.g., histamine, prostaglandins, cytokines) are released to orchestrate the inflammatory response.

a. Chronic Inflammation

- **Onset:** Gradual onset.
- **Duration:** Prolonged (weeks to years).
- **Key Features:** Persistent inflammation with tissue destruction and healing occurring simultaneously.
- **Mechanisms:**
  - **Persistent Inflammation:** Continuous presence of irritants or pathogens leads to prolonged activation of the immune system.
  - **Cellular Infiltrate:** Involves a mix of macrophages, lymphocytes, and plasma cells.
  - **Fibrosis:** Chronic inflammation can lead to excessive connective tissue formation, resulting in scar tissue.

2. Repair

Repair is the process by which tissue architecture and function are restored following injury. This process can occur via regeneration or fibrosis.

Repair Mechanisms

a. Regeneration

- **Definition:** Replacement of lost tissue with the same type of cells, restoring normal function.
- **Process:**
  - **Cell Proliferation:** Cells divide to replace damaged or lost cells.
  - **Tissue Regeneration:** Tissue architecture is restored to its normal state.

b. Fibrosis (Scar Formation)

- **Definition:** Replacement of damaged tissue with fibrous connective tissue (scar tissue) when regeneration is not possible.
- **Process:**
  - **Angiogenesis:** Formation of new blood vessels to supply the growing tissue.
  - **Fibroblast Proliferation:** Fibroblasts produce collagen and extracellular matrix components to form the scar.
  - **Scar Maturation:** The initial granulation tissue matures into a fibrous scar with reduced cellularity and increased collagen deposition.

Key Factors Influencing Repair:

1. **Type and Extent of Injury:** The severity and type of injury affect the repair process and outcomes.
2. **Tissue Type:** Different tissues have varying capacities for regeneration (e.g., skin vs. cardiac muscle).
3. **Systemic Factors:** Age, nutritional status, and overall health can impact the repair process.

Overall Integration

The inflammatory response and repair process are tightly regulated to ensure proper healing and restoration of tissue function. Dysregulation in these processes can lead to chronic inflammation, impaired healing, and disease development. Understanding these mechanisms provides insights into various pathologies and guides therapeutic strategies for managing inflammation and promoting effective tissue repair.

II. CLINICAL SIGNS OF INFLAMMATION

The classical signs of inflammation, first described by Aulus Cornelius Celsus in the 1st century AD, are:

1. **Redness (Rubor):** This occurs due to the dilation of small blood vessels within the damaged area.
2. **Heat (Calor):** An increase in temperature is seen in the inflamed area, which is also a result of increased blood flow.
3. **Swelling (Tumor):** This is caused by the accumulation of fluid outside the blood vessels.
4. **Pain (Dolor):** This can be due to the release of chemicals that stimulate nerve endings or the increased pressure on nerve endings from the swelling.
5. **Loss of Function (Functio Laesa):** This can be a result of pain or severe swelling, which inhibits the normal function of the tissue.

Basic Mechanism of Inflammation and Repair

1. **Recognition of Injury or Infection**
   a. Pathogen Recognition
   - **Receptors:** Pathogen Recognition Receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs).
   - **Function:** Detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) to initiate an inflammatory response.

   b. Endothelial Cell Activation:
   - **Stimuli:** Inflammatory cytokines (e.g., TNF-α, IL-1).
   - **Effect:** Upregulation of adhesion molecules (e.g., selectins, integrins), leading to increased leukocyte adhesion and migration.

2. **Vascular Changes:**
   a. **Vasodilation:**
      - **Mediators:** Histamine, prostaglandins.
      - **Effect:** Increases blood flow to the affected area, causing redness (rubor) and heat (calor).
   b. **Increased Vascular Permeability:**
      - **Mediators:** Histamine, bradykinin, leukotrienes.
      - **Effect:** Endothelial cell contraction or damage, allowing fluid, proteins, and cells to leak into the tissue, causing swelling (tumor).

3. **Leukocyte Recruitment and Activation:**
   a. **Chemotaxis:**
      - **Chemotactic Factors:** C5a, LTB4, IL-8.
      - **Function:** Directs leukocytes to the site of injury or infection.
   b. **Leukocyte Adhesion and Migration:**
      - **Selectins:** Mediate rolling of leukocytes on the endothelium.
      - **Integrins:** Facilitate firm adhesion of leukocytes to the endothelium.
      - **PECAM-1 (CD31):** Assists in transmigration of leukocytes through the endothelium.
   c. **Phagocytosis:**
      - **Phagocytes:** Neutrophils, macrophages.
      - **Process:** Engulfment and destruction of pathogens and debris, enhanced by opsonization.

4. **Removal of the Injurious Agent**
   a. **Degranulation**
      - **Cells:** Mast cells, neutrophils.
      - **Mediators:** Release of histamine, enzymes, and other inflammatory mediators.
   b. **Production of Reactive Oxygen Species (ROS):**
      - **Source:** Neutrophils and macrophages.
      - **Function:** Kill pathogens but can also contribute to tissue damage if excessive.
   c. **Release of Enzymes:**
      - **Examples:** Proteases, lipases.
      - **Function:** Break down extracellular matrix components and pathogens.

5. **Resolution of Inflammation**
   a. **Anti-inflammatory Mediators**
      - **Cytokines:** IL-10, TGF-β.
      - **Lipoxins, Resolvins:** Produced to counteract inflammation and promote healing.
   b. **Apoptosis of Neutrophils**
      - **Process:** Programmed cell death followed by clearance by macrophages.
   c. **Phagocytosis of Apoptotic Cells**
      - **Macrophages:** Engulf and clear apoptotic cells and debris.

6. **Tissue Repair**
   a. **Regeneration**
      - **Process:** Replacement of damaged cells with the same cell type, restoring normal function.

b. Fibrosis
- **Formation:** Deposition of collagen and extracellular matrix components by fibroblasts.
- **Mediators:** TGF-β, fibroblast growth factor (FGF).

c. Angiogenesis
- **Growth Factors:** VEGF, FGF.
- **Function:** Formation of new blood vessels to supply nutrients and oxygen.

d. Remodeling
- **Process:** Matrix metalloproteinases (MMPs) remodel the ECM to restore normal tissue architecture.

Clinical Signs of Inflammation

The clinical signs of inflammation are direct manifestations of the underlying inflammatory processes and can vary depending on the location and extent of the inflammation. They are typically summarized as:

1. **Redness (Rubor)**
   a. **Cause:** Increased blood flow to the affected area due to vasodilation.
   b. **Mechanism:** Prostaglandins and histamine induce vasodilation, leading to an influx of blood.
2. **Heat (Calor)**
   a. **Cause:** Increased blood flow (hyperemia) to the inflamed area.
   b. **Mechanism:** Similar to redness, vasodilation results in increased blood flow, raising the local temperature.
3. **Swelling (Tumor)**
   a. **Cause:** Accumulation of fluid (edema) and cells in the interstitial tissue.
   b. **Mechanism:** Increased vascular permeability allows fluid, proteins, and cells to leak into the tissue.
4. **Pain (Dolor)**
   a. **Cause:** Release of pain-inducing mediators and increased pressure from swelling.
   b. **Mechanism:** Prostaglandins and bradykinin sensitize nerve endings, and the pressure from swelling stimulates pain receptors.
5. **Loss of Function (Functio laesa)**
   a. **Cause:** Pain, swelling, and tissue damage affect normal function.
   b. **Mechanism:** Pain and swelling limit movement or function of the affected area, and tissue damage can impair organ function.

Molecular Mediators of Inflammation and Repair

Molecular mediators play crucial roles in the regulation and progression of inflammation and tissue repair. They include cytokines, chemokines, eicosanoids, and growth factors, each contributing to different aspects of the inflammatory response and repair processes.

1. **Cytokines**
   a. **Tumor Necrosis Factor-alpha (TNF-α)**
      - **Source:** Macrophages, T-cells, and other cells.
      - **Function:** Promotes inflammation by inducing fever, activating endothelial cells, and stimulating the production of other cytokines.
   b. **Interleukin-1 (IL-1)**
      - **Source:** Macrophages, endothelial cells.

- **Function:** Similar to TNF-α, it promotes inflammation and fever, and enhances the expression of adhesion molecules on endothelial cells.

c. Interleukin-6 (IL-6)
- **Source:** Macrophages, T-cells.
- **Function:** Stimulates the acute phase response, leading to increased production of acute-phase proteins by the liver.

d. Interleukin-10 (IL-10)
- **Source:** Macrophages, T-cells.
- **Function:** Anti-inflammatory cytokine that inhibits the production of pro-inflammatory cytokines and promotes resolution of inflammation.

e. Transforming Growth Factor-beta (TGF-β)
- **Source:** Macrophages, fibroblasts.
- **Function:** Regulates the immune response and promotes fibrosis and tissue repair.

2. Chemokines

a. Interleukin-8 (IL-8)
- **Source:** Macrophages, endothelial cells.
- **Function:** Attracts neutrophils to the site of inflammation through chemotaxis.

b. Monocyte Chemoattractant Protein-1 (MCP-1 or CCL2)
- **Source:** Macrophages, endothelial cells.
- **Function:** Recruits monocytes to sites of inflammation.

3. Eicosanoids

a. Prostaglandins:
- **Source:** Produced from arachidonic acid by cyclooxygenase enzymes (COX-1 and COX-2).
- **Function:** Mediate pain, fever, and vasodilation; some also contribute to the resolution of inflammation.

b. Leukotrienes:
- **Source:** Produced from arachidonic acid by lipoxygenase enzymes.
- **Function:** Promote leukocyte adhesion, increase vascular permeability, and contribute to bronchoconstriction in asthma.

c. Thromboxanes:
- **Source:** Platelets.
- **Function:** Promote platelet aggregation and vasoconstriction.

4. Growth Factors

a. Vascular Endothelial Growth Factor (VEGF):
- **Source:** Macrophages, fibroblasts.
- **Function:** Stimulates angiogenesis (formation of new blood vessels) to support tissue repair.

b. Fibroblast Growth Factor (FGF):
- **Source:** Fibroblasts, endothelial cells.
- **Function:** Promotes fibroblast proliferation and tissue repair.

c. Platelet-Derived Growth Factor (PDGF):
- **Source:** Platelets, macrophages.
- **Function:** Stimulates fibroblast proliferation and collagen production, contributing to tissue repair and fibrosis.

Clinical Signs of Inflammation and Their Molecular Mediators

1. **Redness (Rubor):**
   a. **Mediators:** Prostaglandins (e.g., PGE2), nitric oxide (NO).
   b. **Mechanism:** Prostaglandins and NO cause vasodilation, increasing blood flow to the affected area.
2. **Heat (Calor):**
   a. **Mediators:** Prostaglandins, histamine.
   b. **Mechanism:** Increased blood flow and metabolic activity result in elevated local temperature.
3. **Swelling (Tumor):**
   a. **Mediators:** Histamine, bradykinin, leukotrienes.
   b. **Mechanism:** Increased vascular permeability allows fluid, proteins, and cells to leak into the tissue.
4. **Pain (Dolor):**
   a. **Mediators:** Prostaglandins, bradykinin.
   b. **Mechanism:** Prostaglandins and bradykinin sensitize pain receptors, contributing to the sensation of pain.
5. **Loss of Function (Functio laesa):**
   a. **Mediators:** Overall impact of pain, swelling, and tissue damage.
   b. **Mechanism:** Pain and swelling reduce mobility and function, while tissue damage impairs normal function.

III. DIFFERENT TYPES OF INFLAMMATION

Inflammation can be classified based on its duration, underlying cause, and the type of immune response involved. The main types of inflammation are acute and chronic inflammation, each with distinct characteristics and mechanisms.

Acute Inflammation

Acute inflammation is the body's immediate and early response to injury or infection, characterized by rapid onset and short duration. It aims to eliminate the cause of injury, clear damaged tissues, and initiate tissue repair. Here's a detailed look at acute inflammation and its mechanisms.

Key Features of Acute Inflammation

1. **Onset and Duration:**
   a. **Onset:** Rapid, occurring within minutes to hours.
   b. **Duration:** Short-term, usually resolving within a few days.
2. **Clinical Signs:**
   a. **Redness (Rubor):** Due to increased blood flow (hyperemia).
   b. **Heat (Calor):** Also due to increased blood flow.
   c. **Swelling (Tumor):** Due to increased vascular permeability and edema.
   d. **Pain (Dolor):** Resulting from the release of pain-inducing mediators and pressure from swelling.
   e. **Loss of Function (Functio laesa):** Due to pain and tissue damage.

Basic Mechanisms Involved in Acute Inflammation

1. **Recognition of Injury or Infection**
   a. **Pathogen Recognition Receptors (PRRs)**
      - **Examples:** Toll-like receptors (TLRs), NOD-like receptors (NLRs).
      - **Function:** Recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), initiating the inflammatory response.
   b. **Endothelial Cell Activation**
      - **Stimuli:** Cytokines like TNF-α and IL-1.
      - **Effect:** Upregulation of adhesion molecules (e.g., selectins, integrins) on endothelial cells, facilitating leukocyte adhesion.

2. **Vascular Changes**
   a. **Vasodilation**
      - **Mediators:** Histamine, prostaglandins.
      - **Effect:** Increases blood flow to the affected area, causing redness and heat.
   b. **Increased Vascular Permeability**
      - **Mediators:** Histamine, bradykinin, leukotrienes.
      - **Effect:** Endothelial cells contract or become damaged, allowing fluid, proteins, and leukocytes to leak into the tissue, causing swelling (edema).

3. **Leukocyte Recruitment and Activation**
   a. **Chemotaxis**
      - **Chemotactic Factors:** C5a, LTB4, IL-8.
      - **Function:** Directs leukocytes to the site of injury or infection.
   b. **Leukocyte Adhesion**
      - **Selectins:** Mediate rolling of leukocytes on the endothelium.
      - **Integrins:** Facilitate firm adhesion to the endothelium.
      - **PECAM-1 (CD31):** Assists in transmigration of leukocytes through the endothelium.
   c. **Phagocytosis**
      - **Phagocytes:** Neutrophils, macrophages.
      - **Process:** Engulfment and destruction of pathogens and debris. Enhanced by opsonization (coating of pathogens with opsonins like C3b and antibodies).

4. **Removal of the Injurious Agent**
   a. **Degranulation**
      - **Cells:** Mast cells, neutrophils.
      - **Mediators:** Release of histamine, enzymes, and other inflammatory mediators.
   b. **Production of Reactive Oxygen Species (ROS):**
      - **Source:** Neutrophils and macrophages.
      - **Function:** Kill pathogens but can also contribute to tissue damage if excessive.
   c. **Release of Enzymes:**
      - **Examples:** Proteases, lipases.
      - **Function:** Break down extracellular matrix components and pathogens.

5. **Resolution of Inflammation**
   a. **Anti-Inflammatory Mediators**
      - **Cytokines:** IL-10, TGF-β.

- **Lipoxins, Resolvins:** Produced to counteract the inflammatory response and promote healing.

b. Apoptosis of Neutrophils

- **Process:** Programmed cell death of neutrophils followed by clearance by macrophages.

c. Phagocytosis of Apoptotic Cells

- **Macrophages:** Engulf and clear apoptotic cells and debris, preventing secondary inflammation.

Types of Acute Inflammation

1. **Serous Inflammation**
   a. **Characteristics:** Fluid accumulation with low protein content.
   b. **Examples:** Blister formation, serous effusions.
2. **Fibrinous Inflammation**
   a. **Characteristics:** Fibrin deposition in the extracellular space.
   b. **Examples:** Pericarditis, fibrinous pleuritis.
3. **Purulent (Suppurative) Inflammation**
   a. **Characteristics:** Accumulation of pus (neutrophils, dead cells, and fluid).
   b. **Examples:** Abscesses, bacterial infections.
4. **Hemorrhagic Inflammation**
   a. **Characteristics:** Presence of blood in the inflammatory exudate.
   b. **Examples:** Severe infections, trauma.

Chronic Inflammation

Chronic inflammation is a prolonged inflammatory response that can last for months or years. It often results from the failure to eliminate the cause of acute inflammation or from a continuous exposure to an injurious agent. Chronic inflammation is characterized by the presence of macrophages, lymphocytes, and plasma cells, and it leads to tissue destruction and repair.

Key Features of Chronic Inflammation

1. **Onset and Duration:**
   a. **Onset:** Gradual, can follow acute inflammation or occur insidiously.
   b. **Duration:** Long-term, lasting months to years.
2. **Clinical Signs:**
   a. **Persistent Symptoms:** May include fatigue, weight loss, and low-grade fever.
   b. **Localized Effects:** Dependent on the affected organ or tissue, such as chronic cough in chronic bronchitis or abdominal pain in inflammatory bowel disease.

Basic Mechanisms Involved in Chronic Inflammation

1. **Ongoing Injury or Insult**
   a. **Persistent Pathogen or Antigen:** Continued presence of microorganisms (e.g., tuberculosis) or foreign bodies (e.g., splinters).
   b. **Autoimmune Reactions:** The immune system attacks normal tissues (e.g., rheumatoid arthritis).

2. **Cellular Infiltration**
   a. **Macrophages**
      - **Role:** Dominant in chronic inflammation, they phagocytize pathogens, dead cells, and debris.
      - **Activation:** Macrophages can be classically activated (M1) to produce pro-inflammatory cytokines or alternatively activated (M2) to promote tissue repair and fibrosis.
   b. **Lymphocytes**
      - **Types:** T-cells (CD4+, CD8+), B-cells.
      - **Function:** Produce cytokines, provide help to macrophages, and mediate adaptive immune responses.
   c. **Plasma Cells**
      - **Origin:** Differentiated B-cells.
      - **Function:** Produce antibodies against persistent antigens.

3. **Tissue Destruction and Repair**
   a. **Continued Damage:** Persistent inflammation leads to ongoing tissue destruction.
   b. **Fibrosis:** Excessive deposition of collagen and extracellular matrix components by fibroblasts. This results in scar formation and loss of normal tissue architecture.
      - **Mediators:** Transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF).

4. **Granuloma Formation**
   a. **Definition:** A specialized form of chronic inflammation where macrophages aggregate to form granulomas, often surrounded by a fibrous capsule.
   b. **Types**
      - **Caseating Granulomas:** Characterized by central necrosis, seen in tuberculosis.
      - **Non-caseating Granulomas:** Without central necrosis, seen in sarcoidosis.
   c. **Purpose:** To isolate and contain the persistent antigen or pathogen.

5. **Mediators of Chronic Inflammation**
   a. **Cytokines**
      - **Examples:** Interferon-gamma (IFN-γ), Tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6).
      - **Function:** Promote and sustain inflammation by activating macrophages and lymphocytes.
   b. **Chemokines**
      - **Examples:** CCL2 (MCP-1), CXCL9.
      - **Function:** Recruit leukocytes to the site of inflammation.
   c. **Growth Factors**
      - **Examples:** Vascular endothelial growth factor (VEGF), TGF-β.
      - **Function:** Promote angiogenesis and fibrosis.

6. **Resolution and Repair**
   a. **Impaired Resolution:** In chronic inflammation, the mechanisms that normally resolve inflammation are often overwhelmed or impaired.
   b. **Healing:** May involve fibrosis and scar formation if regeneration is not possible. Chronic inflammation can lead to functional impairment and structural changes in affected tissues.

Types of Chronic Inflammation

1. **Chronic Active Inflammation**
   a. **Characteristics:** Ongoing inflammation with active tissue destruction and repair.
   b. **Examples:** Chronic infections, autoimmune diseases.
2. **Chronic Granulomatous Inflammation**
   a. **Characteristics:** Formation of granulomas.
   b. **Examples:** Tuberculosis, sarcoidosis, Crohn's disease.
3. **Chronic Fibrosing Inflammation**
   a. **Characteristics:** Excessive fibrosis and scarring.
   b. **Examples:** Pulmonary fibrosis, liver cirrhosis.

IV. MECHANISM OF INFLAMMATION

Alteration in Vascular Permeability and Blood Flow

Vascular Changes in Inflammation

1. **Vasodilation**
   a. **Initial Vasoconstriction:** Brief and transient, typically lasting only a few seconds.
   b. **Subsequent Vasodilation:** Mediated by histamine, nitric oxide, and other vasoactive mediators, leading to increased blood flow (hyperemia) and the classic signs of redness (rubor) and heat (calor).

2. **Increased Vascular Permeability**
   a. **Immediate Transient Response:** Occurs within minutes and is mediated by histamine and bradykinin, causing endothelial cells to contract and form gaps.
   b. **Delayed Prolonged Response:** Mediated by cytokines such as TNF-α and IL-1, leading to retraction of endothelial cells over hours to days.
   c. **Direct Endothelial Injury:** Can cause sustained leakage due to endothelial cell necrosis or detachment, often seen in severe burns or infections.

3. **Stasis and Margination**
   a. **Stasis:** Blood flow slows down due to increased vascular permeability, resulting in more concentrated blood cells.
   b. **Margination:** Leukocytes move toward and adhere to the endothelial lining of the blood vessels.

4. **Leukocyte Extravasation**
   a. **Rolling:** Selectins on endothelial cells and leukocytes facilitate a rolling interaction.
   b. **Adhesion:** Integrins on leukocytes bind to intercellular adhesion molecules (ICAMs) on endothelial cells.
   c. **Transmigration (Diapedesis):** Leukocytes pass through the endothelial layer and basement membrane into the tissue.

Basic Mechanism Involved in the Process of Inflammation and Repair

1. **Recognition of the Injurious Agent:**
   a. **Pathogen Recognition Receptors (PRRs)**
      - PRRs such as Toll-like receptors (TLRs) on macrophages and dendritic cells recognize PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns).

2. **Recruitment of Leukocytes**
   a. **Chemotaxis**
      - Chemokines and other chemotactic factors direct the migration of leukocytes to the site of injury.
      - C5a, leukotriene B4, and bacterial products are common chemotactic agents.
   b. **Leukocyte Adhesion and Migration**
      - **Selectins:** Mediate weak, rolling interactions.
      - **Integrins:** Mediate firm adhesion to the endothelium.
      - **PECAM-1 (Platelet Endothelial Cell Adhesion Molecule-1):** Facilitates transmigration of leukocytes.

3. **Removal of the Injurious Agent**
   a. **Phagocytosis**
      - Neutrophils and macrophages engulf pathogens and debris.
      - Phagocytosis is enhanced by opsonins such as antibodies and complement proteins (e.g., C3b).
   b. **Degranulation and Release of Mediators**
      - Mast cells and basophils release histamine and other granules containing inflammatory mediators.
      - Activated macrophages and neutrophils release reactive oxygen species (ROS) and enzymes to kill pathogens.

4. **Resolution of Inflammation**
   a. **Anti-Inflammatory Cytokines**
      - IL-10 and TGF-β play crucial roles in dampening the inflammatory response.
      - Lipoxins, resolvins, and protectins also contribute to the resolution phase.
   b. **Apoptosis and Clearance of Neutrophils**
      - Neutrophils undergo apoptosis and are phagocytosed by macrophages.

5. **Tissue Repair**
   a. **Regeneration**
      - If the injury is mild and the tissue has a high proliferative capacity (e.g., epithelial cells), regeneration occurs.
   b. **Fibrosis (Scar Formation)**
      - When regeneration is not possible, fibroblasts proliferate and deposit extracellular matrix (ECM) components, leading to scar formation.
   c. **Angiogenesis**
      - New blood vessels form to supply nutrients and oxygen to the healing tissue.
      - Mediated by growth factors such as VEGF (vascular endothelial growth factor).
   d. **Remodeling**
      - ECM is remodeled by matrix metalloproteinases (MMPs) to restore normal tissue architecture.

Molecular Mediators of Inflammation and Repair:

1. **Vasoactive Amines**
   a. **Histamine:** Released by mast cells and basophils, causing vasodilation and increased vascular permeability.
   b. **Serotonin:** Released by platelets, also contributing to vasodilation and increased permeability.

2. **Eicosanoids**
   a. **Prostaglandins:** Mediate vasodilation, fever, and pain.
   b. **Leukotrienes:** Increase vascular permeability and leukocyte chemotaxis.

3. **Cytokines**
   a. **TNF-α and IL-1:** Promote leukocyte recruitment and activation, as well as endothelial activation.

4. **Complement System**
   a. **C3a and C5a:** Anaphylatoxins that increase vascular permeability and attract leukocytes.

5. **Growth Factors**
   a. **EGF (Epidermal Growth Factor), FGF (Fibroblast Growth Factor), VEGF:** Stimulate cell proliferation, differentiation, and angiogenesis.